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For: NASAL CALCITONIN FORMULATION

Commissioner for Patents
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COMMU NICATION

Sir:

Submitted herewith is a copy of the translation of Japanese Patent Application Number: Toku Kai Hei 5-78258, which has already been cited in an Information Disclosure Statement mailed December 2, 2004, and which is provided for the convenience of the Examiner.

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(54) (Title of Invention) Stable Calcitonin Medicinal Composition and a Method for Its Preparation
(57) (Summary)
(Objective) To offer a liquid medicinal composition that contains a comparatively high concentration of calcitonin and that is difficultly condensed during its storage.

(Constitution)

A medicinal composition with calcitonin as an effective ingredient, containing, as a stabilizing agent, citric acid or either one or a plurality of (1) citric acid and (2) polyvinyl alcohol, polyoxyethylene sorbitan fatty acid ester and polyoxy hard castor oil.

(Scope of Claim for Patent)

(Claim 1) A medicinal composition with calcitonin as an effective ingredient, characterized in that it contains, as a stabilizing agent, citric acid and either one or a plurality of polyvinyl alcohol, polyoxyethylene sorbitan fatty acid ester and polyoxy ethylene hard castor oil.

(Claim 2) A medicinal composition with calcitonin as an effective ingredient, characterized in that it contains, as a stabilizing agent, citric acid or (1) citric acid and (2) either one or a plurality of polyvinyl alcohol, polyoxy ethylene sorbitan fatty acid ester and polyoxy ethylene hard castor oil.

(Claim 3) A method for the preparation of a liquid medicinal composition that contains calcitonin, with citric acid being added thereto as a stabilization agent.

(Claim 4) A method for the preparation of a liquid medicinal composition that contains calcitonin, characterized in that one or a plurality of citric acid, polyvinyl alcohol, polyoxy ethylene sorbitan fatty acid ester and polyoxy ethylene hard castor oil is added as a stabilization agent.

(Claim 5) A method for the preparation of a liquid medicinal composition containing calcitonin, characterized in that, as a stabilization agent, citric acid is added or (1) citric acid and (2) either one or a plurality of polyvinyl alcohol, polyoxy ethylene sorbitan fatty acid ester and polyoxyethylene hard castor oil is added.

(Detailed Explanation of the Invention)

(0001)

(Field of Utilization in the Industry)

This invention relates to a stable calcitonin medicinal composition and a method for its preparation.

(0002)

(Conventional Technology And Problem To Be Solved)

Calcitonin is employed in the treatment of osteoporosis to relieve pains, high calcium in blood and Paget's disease and so forth. It is a polypeptide hormone that possesses a variety of pharmacological activities. Calcitonin is administered by injection under normal conditions. Depending upon the conditions, it is necessary to administer it for a long period of time on a continuous basis. There is a demand for its administration by means other than through injections. Its administration through the nostril is one of such means. In such a case, it is desirable that the dosage for one-time administration be less than 0.2 or 0.3 milliliters. If the amount of the dosage happens to be large, it tends to leak from the nostril, thereby preventing its effective administration.

(0003)

Accordingly, the medicinal solution of comparatively a high concentration is needed to give an effective treatment dosage. In the case of human calcitonin, for instance, it is necessary to prepare a medicinal solution of 0.5 milligrams per milliliter or more. Nevertheless, calcitonine tends to condense in a solution, with its condensation taking place particularly easily by mechanical stress, It becomes unstable as its density rises and, it is difficult to prepare the solution of a desirable calcitonin density stably so as to make it desirable for a medical treatment.

(0004)

If the medicinal solution produces milky precipitates because of condensation, it becomes impossible to give a uniform administration and its absorption through the nostril is markedly hampered. Gelatin, albumin and some surface active agents have been reported to have an effect on the prevention of the condensation of protein and peptide. Nevertheless, it has been impossible to prepare a calcitonin medicinal composition and a calcitonin solution which is practical and stable with little local stimulation.

(0005)

(Means For The Solution Of The Problem)

The current inventors have carried out a series of examinations on the stabilization of the calcitonin solution by the addition of various additives that are permissible for medical use. This invention was culminated upon the discovery that a stable and easily absorbable calcitonin solution as well as calcitonin medical compositions in such concentrations as would be desirable for medical treatment can be prepared by mixing certain kinds of additives.

(0006)

In other words, this invention relates to a method for the preparation of a stable calcitonin medicinal composition and a calcitonin solution. It is characterized in that it contains, as a stabilizing agent, one or a plurality of citric acid, polyvinyl alcohol, polyoxy ethylene sorbitan fatty acid ester and polyoxy ethylene hardened castor oil.

(0007)

Stabilization agents (citric acid, in particular) are believed to be effective when they are employed

individually. However, it is desirable for same to contain (1) citric acid and one or a plurality of (2) polyvinyl alcohol, polyoxy ethylene sorbitan fatty acid ester and polyoxy ethylene hardened castor oil. More preferably, it is desirable to use, among these combinations, a combination of citric acid and polyvinyl alcohol, a combination of citric acid and polyoxy ethylene sorbitan fatty acid ester or a combination of citric acid and polyoxy ethylene hardened castor oil. Through the addition of these stabilization agents to the calcitonin medicinal composition or the calcitonin solution, the effect of high stabilization can be obtained.

(0008)

According to this invention, citric acid is added to and mixed with the medicinal solution ordinarily in an amount of 0.05 through five per cent (W/V) and preferably one to two per cent (W/V). Polyvinyl alcohol is a synthesized high polymer which is obtained by the radical polymerization of vinyl acetate and it is added in such an amount that it will ordinarily be in the range between 0.001 and 10 per cent (W/V) and preperably between 0.01 and five per cent (W/V) as compared with the medicinal solution.

Polyoxy ethylene sorbitan fatty acid ester is a non-ionic surface active agent obtained by the additive polymerization of sorbitan fatty acid ester and ethylene oxide. For example, Polysorbate-40 and Polysorbate-60, as well as Polysorbate-80, etc. can be mentioned.

(0009)

Polyoxyethylene sorbitan fatty acid ester is added in such an amount that it will ordinarily be in the

range between 0.001 and one per cent (W/V) and preferably between 0.005 and 0.5 per cent (W/V) as compared with the medicinal solution. Polyoxy ethylene hardened castor oil is a non-ionic surface active agent which is obtained by the additive polymerization of ethylene oxide with a hardened oil that is obtained by adding hydrogen to castor oil. For example, Niccor HCO-10, Niccor HCO-40, Niccor HCO-50 and Niccor HCO-60 and so forth can be mentioned.

Polyoxy ethylene hardened castor oil is added in such an amount as will ordinarily be in the range between 0.001 and one per cent (W/V) and preferably between 0.005 and 0.5 per cent (W/V) as compared with the medicinal solution.

(0010)

The medicinal composition according to this invention can be in the form of a solution or in the form of a powder that can be used by dissolving same with some specific solution. In the case of a powder that is dissolved as the occasion requires into a solution, citric acid, polyvinyl alcohol, polyoxy ethylene sorbitan fatty acid ester and/or polyoxy ethylene hardened castor oil may be added either to the powder or the solution or may be added to both of them.

(0011)

It is possible to add a pH adjuster, a sterilizer, an antiseptic, a viscosity adjuster, a freezing or drying agent, or an absorption promotor as the occasion demands. As the pH adjusters, hydrochloric acid and acetic acid, etc. can be used. As the antiseptic or sterilizer, anything that is ordinarily used for the medicinal compositions can be used, including paraoxy benzoic acid ester and chlorinated benzalkonium,

etc.

In addition, polyvinyl pyrrolidone and hydroxy propyl methyl cellulose and so forth can be mentioned as the viscosity adjusting agents.

(0012)

As the freezing and drying agents, amino acetic acid, mannitol, white sugar, dextrose and dextran , and so forth can be mentioned.

As the absorption promoting agents, sodium caprate, bestatin, amastatin, naphamostat mesilate, camostat mesilate, aprotin, etc. can be mentioned.

(0013)

Regarding the manner of administering the medicinal compositions according to this invention, either a solution or a medicinal solution obtained by dissolving a powder at the time when it is to be used can be administered through dripping or spraying by using a container for nostril administration, a spray case or a nostril aerosol applicator, etc.

The calcitonin that can be used in this invention comes from humans, pigs, cows, salmons, eels and rats, etc. and, as such, it is not restricted as to its origin, in particular. However, human calcitonin is used in the examples which will be shown below:

(0014)

(Examples)

Below, this invention will be explained in detail using examples and tests. However, this invention is not to be restricted to these examples alone.

Example 1: Human calcitonin	20 mg
Refined white sugar	1000 mg
Chlorinated benzalconium	2 mg
Stabilization agent (citric acid)	15 mg

Purified water was added so that the final volume would be 10 milliliters.

(0015) Example 2

Human calciton	20 mg
Refined white sugar	1000 mg
Chlorinated benzalkonium	2 mg
Stabilizing agent (polyvinyl alcohol)	100 mg

Purified water was added so that the final volume would be 10 milliliters.

(0016) Example 3

Human calcitonin	20 mg
Refined white sugar	1000 mg
Chlorinated benzalkonium	2 mg
Stabilization agent (polysorbate 80)	10 mg

Purified water was added so that the final volume would be 10 milliliters.

(0017) Example 4

Human calcitonin	20 mg
Mannitol	500 mg
Chlorinated benzalkonium	2 mg
Stabilization agent (citric acid)	15 mg

Purified water was added so that the final volume would be 10 milliliters.

(0018) Example 5

Human calcitonin	20 mg
Mannitol	500 mg
Chlorinated benzalkonium	2 mg
Stabilizing agent (polyvinyl alcohol)	100 mg

Purified water was added so that the final volume would be 10 milliliters.

(0019) Example 6

Human calcitonin	20 mg
Mannitol	500 mg
Chlorinated benzalkonium	2 mg
Stabilization agent (Polysorbate 80)	10 mg

Purified water was added so that the final volume would be 10 milliliters.

(0020) Example 7

Human calcitonin	20 mg
Refined white sugar	1000 mg
Chlorinated benzalkonium	2 mg
Stabilization agent (citric acid)	60 mg
Stabilization agent (polyvinyl alcohol)	100 mg

Purified water was added so that the final volume would be 10 milliliters.

(0021) Example 8

Human calcitonin	20 mg
Refined white sugar	1000 mg
Chlorinated benzalkonium	2 mg
Stabilizing agent (citric acid)	60 mg
Stabilizing agent (Polysorbate 80)	1 mg

Purified water was added so that the final volume would be 10 milliliters.

(0022) Example 9

Human calcitonin	20 mg
Refined white sugar	1000 mg
Chlorinated benzalkonium	2 mg
Stabilization agent (citric acid)	60 mg
Stabilization agent (polyoxy ethylene hardened castor oil*1)	1 mg

Purified water was added to make the final volume 10 milliliters.

*1: Niccor HCO-60 (Nikko Chemical Company, Limited)

(0023) Example 10

Human calcitonin	20 mg
Refined white sugar	1000 mg
Chlorinated benzalkonium	2 mg
Stabilization agent (citric acid)	60 mg
Stabilization agent (polyvinyl alcohol)	100 mg
Aprotinin	1 mg

Purified water was added so that the final volume would be 10 milliliters.

(0024) Example 11

Human calcitonin	20 mg
Refined white sugar	1000 mg
Chlorinated benzalkonium	2 mg
Stabilization agent (citric acid)	60 mg
Stabilization agent (Polysorbate 80)	1 mg
Naphamostat mesilate	1 mg

Purified water was added so that the final volume would be 10 milliliters.

(0025) Contrast Example 1

Human calcitonin	20 mg

Purified water was added so that the final volume would become 10 milliliters.

(0026) Contrast Example 2

Human calcitonin	20 mg
Refined white sugar	1000 mg
Chlorinated benzalkonium	2 mg

Purified water was added so that the final volume would be 10 milliliters.

(0027) Contrast Example 3

Human calcitonin	20 mg
Refined white sugar	1000 mg

Chlorinated benzalkonium	2 mg

Refined white sugar was added so that the final volume would become 10 milliliters.

(0028) Comparative Example 1

Human calcitonin	20 mg
Refined white sugar	1000 mg
Chlorinated benzalkonium	2 mg
Additive (taurocholic acid)	100 mg

Purified water was added so that the final volume would become 10 milliliters.

(0029) Comparative Example 2

Human calcitonin	20 mg
Refined white sugar	1000 mg
Chlorinated benzalkonium	2 mg
Additive (deoxycholic acid)	100 mg

Purified water was added so that the final volume would become 10 milliliters.

(0030) Comparative Example 3

Human calcitonin	20 mg
Refined white sugar	1000 mg
Chlorinated benzalkonium	2 mg
Additive (sucrose fatty acid ester *2)	125 mg

Purified water was added so that the final volume would become 10 milliliters.

*2: Ryoto Sugar Ester S1670 (Mitsubishi Kasei Food Company product)

(0031) Comparative Example 4

Human calcitonin	20 mg
Refined white sugar	1000 mg
Chlorinated benzolkonium	2 mg
Additive (Sucrose Fatty Acid Ester *3)	125 mg

Purified water was added so that the final volume would become 10 milliliters.

*3: Ryoto Sugar Ester P1670 (Mitsubishi Kasei Food product)

(0032)

Comparative Example 5

Human calcitonin	20 mg
Mannitol	500 mg
Chlorinated benzalkonium	2 mg
Additive (taurocholic acid)	100 mg

Purified water was added so that the final volume would become 10 milliliters.

(0033) Comparative Example 6

Human calcitonin	20 mg
Mannitol	500 mg
Chlorinated benzalkonium	2 mg
Additive (deoxycholic acid)	100 mg

Purified water was added so that the final volume would become 10 milliliters.

(0034) Comparative Example 7

Human calcitonin	20 mg
Mannitol	500 mg
Chlorinated benzalkonium	2 mg
Additive (Sucrose Fatty Acid Ester *2)	125 mg

Purified water was added so that the final volume would become 10 milliliters.

*2: Ryoto Sugar Ester S1670 (Mitsubishi Kasei Food product)

(0035) Comparative Example 8

Human calcitonin	20 mg
Mannitol	500 mg
Chlorinated benzalconium	2 mg
Additive (Sucrose Fatty Acid Ester *3)	125 mg

Purified water was added so that the final volume would become 10 milliliters.

*3: Ryoto Sugar Ester P 1670 (Mitsubishi Kasei Food product)

(0036) Comparative Example 9

Human calcitonin	20 mg
Refined white sugar	1000 mg
Chlorinated benzalkonium	2 mg
Stabilizing agent (Citric acid)	60 mg
Additive (Human serum albumin)	200 mg

Purified water was added so that the final volume would become 10 milliliters.

(0037) Comparative Example 10

Human calcitonin	20 mg
Refined white sugar	1000 mg
Chlorinated benzalkonium	2 mg
Stabilization agent (citric acid)	60 mg
Additive (gelatin)	100 mg

Purified water was added so that the final volume would become 10 milliliters.

The calcitonin medicinal compositions mentioned above in this invention were extremely stable as shown in Examples 12 through 14 below.

(0038) Example 12

The specimen solutions prepared in Examples 1 through 6, Comparative Examples 1 through 8 and Contrast Examples 1 through 3 were shaken at the rate of 100 times a minute at room temperature, with the amplitude at three centimeters, and their outside appearance was observed. The result obtained is shown in Table 1.

(0039) Table 1

Outside Appearance of Solutions Subsequent to Shaking

	Start	One Day	Three Days
Example 1	O	O	O
Example 2	O	O	X
Example 3	O	O	X
Example 4	O	O	O
Example 5	O	O	X
Example 6	O	O	X

Contrast Example 1	O	X	X
Contrast Example 2	O	X	X
Contrast Example 3	O	X	X

Comparative Example 1	O	X	X
Comparative Example 2	O	X	X
Comparative Example 3	O	X	X
Comparative Example 4	O	X	X
Comparative Example 5	O	X	X
Comparative Example 6	O	X	X
Comparative Example 7	O	X	X
Comparative Example 8	O	X	X

O: Colorless and transparent solution.

X: Condensation is observed.

As is shown in Table 1, the Examples were found stable as compared with the Comparative Examples and Contrast Examples.

(0040) Example 13

The specimen solutions which were prepared in Examples 7 through 11 and Comparative Examples 9 and 10 were shaken at room temperature at the rate of 100/min., three centimeters amplitude and the appearances were observed. The human calcitonin density of the solutions was determined by means of liquid chromatography and the residual human calcitonin rate was obtained. The result obtained

is shown in Table 2.

(0041) Table 2

Outside appearances of solutions after shaking and the residual rates:

	Start	1 day	3 days	7 days	
	Outside Appearance	Outside Appearance	Outside Appearance	Outside Appearance	Rasidual Rate
Example 7	O	O	O	O	96%
Example 8	O	O	O	O	99%
Example 9	O	O	O	O	96%
Example 10	O	O	O	O	98%
Example 11	O	O	O	O	97%

Comparative Example 9	O	X	X	X	-
Comparative Example 10	O	X	X	X	-

O: Colorless and transparent solution.

X: Condensation is observed.

The examples were found stable as compared with the Comparative Examples and Contrast Examples as is shown in Table 2.

(0042) Example 14

The specimen solutions which had been prepared in Examples 7 through 9 were shaken at room temperature at the rate of 100 times per minute, with the amplitude at three centimeters, for a period of seven days. The solutions were then examined as to their biological activities as will be described below:

Male rats (age of six weeks) of the S.D. group, which were forced to fast for a period of 24 hours, followed by feeding with low calcium diet for a period of 24 hours thereafter were back-

wardly fixed under the effect of pentabarbital and were given thigh artery kanule. and trachea kanule. Five (5) U(mu)l of the specimen solution (human calcitonin 50 (mu)g/kg) was administered through the nostril and blood samples were taken from the thigh artery and the serum calcium density was determined by using Sun Assay Ca, a product of Sanko Junyaku Company, Limited for the measurement of calcium. The result obtained is shown in Table 3.

(0043) Table 3

Decrease in the Serum Calcium Density in Rats Which Were Given Human Calcitonin (50 (mu)g per kilogram) Through the Nostrils.

	Decrease in Density of Serum Calcium		
	In 1 Hour	In 2 Hours	In 3 Hours
Example 7	80.4 %	73.2 %	87.6 %
Example 8	82.8 %	68.2 %	64.4 %
Example 9	85.2 %	73.7 %	66.1 %

Rate of Decrease (%) = (Calcium density after the administration)/(calcium density before the administration) x 100.

As is shown in Table 3, a drop in the serum calcium density was observed even in the solutions which were shaken for a period of seven days.

(Effect of the Invention)

This invention offers stable calcitonin medicinal compositions which are practical and stable in a solution, with little local stimulation.